AIDS-associated cholangiopathy: When only the image is not enough

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Abstract: In HIV-infected patients, liver and biliary tract may be affected by different entities, such as AIDS-cholangiopathy, which is usually associated with CD4+ T lymphocytes count below 100 cells/mm³ along with non-specific symptoms. Although imaging studies play a major diagnostic role they should always be evaluated according to patients clinical context. While ultrasound and CT scans provide relevant diagnostic information, specialized studies such as MRI and MRCP have become increasingly valuable due to their ability to demonstrate parietal as well as stenotic biliary changes. Despite ERCP remaining the gold-standard for diagnosis of AIDS-related cholangiopathy, currently it is usually reserved to clearly exclude the presence of malignancy, or as a specific invasive therapeutic procedure, when indicated.

Key words: AIDS, Biliary tract diseases, Endoscopic retrograde cholangiopancreatography (ERCP), HIV, Magnetic resonance imaging (MRI), Sclerosing cholangitis.

Resumen: En pacientes infectados con VIH, el hígado y las vías biliares pueden presentar compromiso de distinta índole. Dentro de éstos, la colangiopatía asociada al SIDA se presenta con una sintomatología más bien inespecífica y habitualmente con recuentos de linfocitos T CD4 <100/mm³. En este escenario, si bien los estudios de imagen juegan un rol muy relevante, éstos siempre deben ser evaluados en relación al contexto clínico del paciente. Si bien la ecografía y la TC aportan valiosa información en el diagnóstico, en la actualidad la resonancia magnética de abdomen combinada con colangi resonancia tienen gran utilidad, por ser capaces de demostrar tanto las alteraciones parietales, como los cambios morfológicos estenóticos biliares de esta patología. Si bien la ERCP aún conserva su valor de gold standard para el diagnóstico, actualmente la tendencia se dirige a reservarla para el descarte de neoplasias, en casos dudosos o como procedimiento terapéutico invasivo específico, cuando sea indicado.

Palabras clave: Colangiopancreatografía endoscópica retrógrada (ERCP), Colangitis esclerosante, Patología de la vía biliar, Resonancia magnética (RM), SIDA, VIH.

Introduction

HIV/AIDS is a global epidemic of which Chile is no stranger. In our country, in December 2008 there was a total of 20,099 notified cases, estimating that on a national level, 50,000 infected people would live with this virus[1]. Although there are significant advances and knowledge in the development and treatment of this pathology, today in Chile it is not uncommon that these patients are investigated at advanced stages of their disease. Thus, the reported rate of HIV in Chile in 2002 was 5.6 patients per 100,000 inhabitants, while AIDS stage patients were approximately 3 cases per 100,000 inhabitants[2]. If we look at the global context, we can appreciate that the epidemiology of this disease has changed, and thanks to the development and dissemination of highly effective antiretroviral therapies, there has been a significant increase in the survival expectancy of these patients[3]. In this way associated pathologies that before probably remained under-diagnosed, have now become more evident.

Within the broad range of manifestations of this disease, hepatic and biliary compromise is not uncommon[4], being observed specifically but not exclusively in immunosuppressed patients[5]. In this group of diseases AIDS-associated cholangiopathy stands out, given that there is little knowledge of it, and the similarity of its imaging patterns with other types of pathologies.

For these reasons we present the following case and review the literature with emphasis on the different forms...
of presentation and their main differential diagnoses.

Case report

Male patient, 21 years old, HIV positive, diagnosed at the age of 19, with lack of adherence to antiretroviral therapy (ART) and multiple hospitalizations due to complications of the original illness, among them several episodes of pneumonia, oropharyngeal candidiasis and a disseminated Kaposi sarcoma.

In the present hospitalization he was admitted with symptoms of right upper quadrant abdominal pain associated with jaundice and CEG. Among the tests performed emphasis is on an abnormal hepatic profile with a cholestatic pattern (alkaline phosphatase and gamma glutamyl transferase [GGT] 8 times above the reference value) and pancytopenia in the blood study. Three months prior to this hospitalization the CD4 T lymphocyte count was less than 20/mm³.

In abdominal ultrasonography, hepatosplenomegaly is described with several small focal hepatic lesions related to disseminated sarcoma, also observing a gallbladder with diffusely thickened walls, without stones and an extrahepatic bile duct without dilatation, but with marked parietal thickening (Figure 1).

In the tomographic tests similar findings are observed, becoming more evident the vesicular edema and annular thickening of the bile duct, associated with the presence of other phenomena related to his original sarcomatous disease (Figure 2). Until this moment, the biliary findings present in all imaging studies were interpreted as an AIDS-associated cholangiopathy.

Figure 1. Gallbladder and spleen involvement in AIDS-associated cholangiopathy. Ultrasound guidance. a) Ultrasound image of the gallbladder with wall thickening (arrowheads). b) Longitudinal ultrasound cut shows normal caliber bile duct (marked with the number 1) and an apparent hepatocholedochus wall thickening (indicated with the number 2).

Figure 2. Contrasted axial CT of the abdomen in AIDS-associated cholangiopathy. A) In portal phase evidence of parietal vesicular edema with mucosa impregnation of same (arrowheads). In the retroperitoneum an adenopathic conglomerate secondary to the disseminated Kaposi sarcoma begins to appear (arrows), which is much more evident at pelvic level (not shown). B) Thickening of the biliary parietal, with significant impregnation of contrast medium (arrowheads).
Abdominal MRI shows similar findings, taking particular attention on the cholangiographic sequences, to the existence of a beaded pattern of the intrahepatic bile duct without interior stones. This study, conducted at another institution, was evaluated separately without medical history or previous tests, considering the diagnosis of sclerosing cholangitis (Figure 3). For administrative and social reasons antiretroviral therapy was not introduced. In subsequent hospitalizations described biliary findings persisted, with severe progress of the visceral compromise of Kaposi sarcoma and associated opportunistic infections. The general condition of the patient was severely compromised, the patient requesting voluntary discharge recorded in the last hospitalization.

Discussion. The biliary disorders described in HIV patients can be classified into three groups: biliary pathology not associated with HIV (e.g. biliary lithiasis), acalculous cholecystitis (AC) and AIDS-associated cholangiopathy (CAS)(4). Below we will refer specifically to the AIDS-associated cholangiopathy, entity first described entity by Guarda, et al 1983(6).

Epidemiology. Although the exact prevalence of CAS is unknown, a study in India showed an incidence of around 1% in HIV-positive patients(7). However, when evaluating these figures consideration has to be taken regarding the fact that this disease is usually observed more frequently in patients who are already at the AIDS stage(4).

Figure 3. Abdominal MRI of AIDS-associated cholangiopathy. a) axial T2 sequence showing thickening and vesicular parietal edema (arrowheads). b) Axial T1 FAT-SAT portal phase post gadolinium acquisition showing the same findings and presence of obvious mucosal impregnation with contrast medium (arrow heads). c) Contrasted coronal T1 FAT-SAT acquisition showing thickening and parietal impregnation of the common bile duct. d, e, f) Cholangiographic sequences. In (d) the already described vesicular edema (arrowheads) and the intrahepatic bile duct alterations (beading) become evident, which are more visible in another orthogonal projection (e) and in a focalized extension of the left biliary tree (arrowheads) of this same image (f).
Pathophysiology and pathogenesis. It is thought that the origin of the CAS is found in repeated opportunistic infections, seeming the bile duct of HIV patients particularly susceptible to these because of, among other factors, a lower secondary pathogen recognition capability, to a reduction in the expression of Toll-like receptors present in the bile duct.

While there is a wide range of pathogens associated with this disease, cytomegalovirus and Cryptosporidium parvum are the agents most frequently associated with the development of this.

It has been proposed that the pathogenesis essential to this disorder would consist in the development of stenosis of the bile duct and the ampulla of Vater after recurrent inflammation episodes of these structures, although a direct action of HIV has also been considered. Biopsies of the Vater’s ampulla in general show submucosal infiltration, periductal inflammation associated with interstitial edema, neutrophilic infiltration and hyperplasia/dilatation of periductal glands.

Diagnosis. The diagnosis for HIV cholangiopathy is rather non-specific. Most patients (90%) present with pain in the right upper quadrant and/or epigastrium. Other symptoms include nausea, vomiting, fever and diarrhea. Jaundice has been described in 10% of patients, but is an uncommon sign to find.

Laboratory. Alterations in liver function tests are often observed, the most often being a cholestatic pattern, with elevated GGT and FA, the latter being around 700-800U/L. Most patients also exhibit a discrete increase in transaminases and total bilirubin, although liver function tests may be found within normal ranges in up to 20% of the cases.

Often, but not exclusively, CAS patients present with CD4 T lymphocyte counts <100/mm³. However, the utility of using the CD4 count as a prognostic factor is under discussion.

Imaging studies. Ultrasound (US) represents the most cost-effective imaging test for initiating the study of CAS patients, showing a sensitivity between 75-97% and a specificity of nearly 100%. Included amongst the most common findings is bile duct dilatation in 70% of cases and wall thickening of the latter in 30% of the patients. Thickening of the gallbladder wall can also be seen and an echogenic nodule at the end of distal common bile duct due to edema of the ampulla of Vater. Computed tomography (CT) of the abdomen can demonstrate dilated intrahepatic biliary better than ultrasound, but it is less sensitive than the latter to detect thickening and stenosis of the common bile duct wall.

The most specific test for the diagnosis of CAS is the endoscopic retrograde cholangiopancreatography (ERCP) which also has the advantage of being therapeutic in some patients. While for ERCP there is a descriptive morphological classification that divides its presentation into four categories, for better understanding, the findings by this method can be grouped into three basic morphological patterns that may occur in isolation or in combination with one another (Figure 4): A) Sclerosing cholangitis pattern. B) Focal papillary stenosis. C) Segmental stenosis (long) of the extrahepatic bile duct.

**Figure 4.** Diagram showing the three basic morphological patterns of stenosis in AIDS-associated cholangiopathy which may occur independently or in combination. a) Intrahepatic sclerosing cholangitis pattern: multiple foci of intrahepatic stenosis with mild segmental dilatation, giving a beaded appearance to the bile duct. This pattern may also include pockets of extrahepatic bile duct stenosis. b) Papillary stenosis: bile duct dilatation secondary to usually less pronounced common bile duct papillary stenosis: may be associated with moderate dilatation of Wirsung duct. c) Long segment stenosis (1-3 cm) of any segment of the extrahepatic bile duct: can be single or multiple.
Papillary stenosis is the isolated event most frequently found (36%). The most common combination is the association of papillary stenosis and the sclerosing cholangitis pattern which is observed in up to 44% of patients. The less frequent pattern is that of long extrahepatic biliary stenosis that affects 5% of the cases\(^1\)\(^2\)\(^3\).

At present, the combined use of magnetic resonance imaging and magnetic resonance cholangiopancreatography (MRCP) are very useful for evaluating both biliary and hepatic parenchymal diseases\(^5\). In these can be seen, the same findings of thickening, edema and parietal biliary capture as described in CT, being able to add in the cholangiographic sequences morphological patterns similar to those described in ERCP\(^1\)\(^5\). The noninvasive nature and good overall performance exhibited by MRCP in the evaluation of biliary disorders, including sclerosing cholangitis, means that some authors suggest their use for diagnostic ends, reserving ERCP for symptomatic treatment of CAS or for ruling out neoplasias using direct histological or cytological studies\(^3\)\(^4\). Finally, there is consensus that the definite diagnosis of CAS be achieved by proper interpretation of medical histories, laboratory findings and imaging patterns\(^4\).

**Differential diagnoses.** The main differential diagnosis of CAS is represented by sclerosing cholangitis\(^1\)\(^5\), since the morphological intrahepatic findings may be indistinguishable from primary sclerosing cholangitis, as evidenced in the case described. Both diseases are characterized by focal stenosis of the bile duct interpersed with moderate segmental dilatation, giving a beaded appearance to the intrahepatic bile ducts\(^1\)\(^5\). To differentiate, it should be noted that pseudodiverticulas in the bile duct walls and high-grade extrahepatic bile duct stenosis, are typical findings of sclerosing cholangitis\(^1\)\(^5\) while moderate ductal dilatation associated with irregular margins and nodules leans more toward CAS\(^1\)\(^3\). Pyogenic cholangitis, another differential diagnosis, usually has a different septic context\(^1\)\(^6\) and is associated with hepatic parenchymal abnormalities (eg peribiliary microabscesses or multifocal perfusion disorders) which the AIDS-associated cholangiopathy lacks.

Distal common bile duct fibrous stenosis secondary to passing of gallstones or chronic pancreatitis represent another possible cause of some of the imaging findings described in CAS\(^1\)\(^5\). To differentiate, it is important to review the medical history and previous studies of the patient.

Finally, other eventual diagnoses to consider include alithiasic cholecystitis and cholangiocarcinoma. However, the clinical context of these is quite different. The first, although it also has a thickened gallbladder wall, occurs in severe septic patients with multiple organ failure or signs of peritonitis. In the second case, we see progressive biliary obstruction in time and with contrasted CT the appearance of infiltrated ductal masses invading the hepatic parenchyma, with delayed capture of contrast medium\(^1\)\(^8\)\(^9\)\(^10\).

**Treatment and prognosis.** The therapy that can be offered to patients with CAS can be divided into symptomatic treatment and treatment for modifying the course of the disease. In the first group we can mention sphincterotomy through ERCP, which provides symptomatic relief to about 90% of patients\(^1\)\(^4\)\(^11\) and is reserved for patients with proven papillary stenosis\(^2\).

The placement of stents in the biliary duct or the dilation of stenotic foci by a balloon might be successful in some patients, although there is no randomized studies to support its use. In addition, ursodeoxycholic acid has been successfully used as an additional symptomatic medical treatment\(^4\).

As for the disease-modifying treatment, the result for CAS has been described to depend largely on the underlying HIV status\(^1\)\(^2\). The median survival of patients with CAS has been described between 9\(^6\) to 34 months\(^6\), which would depend largely on the introduction of ART soon after diagnosis of CAS, if it has not yet begun. CAS development during the course of ART may be a sign of progression of the disease, either by immunosuppression or by resistance to anti-retroviral therapy. Finally, there is relative consensus in that the treatment of opportunistic infections underlying to CAS does not imply symptomatic improvement nor obvious changes in the morphology of the bile duct\(^6\).

Given the above, it is important to emphasize that the presence of intra and/or extra-hepatic biliary stenotic foci in an HIV positive patient makes it necessary to consider the possibility of an AIDS-associated cholangiopathy, which by itself may be an indicator of progression or severity of the disease.

**References**


